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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/963,927	09/26/2001	Thomas Rogers	3391/PCT	1278

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/963,927	ROGERS ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) ___ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group I is acknowledged, as is the elected specie.

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The following is a quotation of the first paragraph of 35 U.S.C. '112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To begin with, it is stipulated that the following claims are enabled:

100. A method of inhibiting angiogenesis comprising administering a compound according to claim 1 to a mammal in need thereof for a time and under conditions effective to antagonize the $\alpha_v\beta_3$ integrin.

101. A method of inhibiting proliferation of tumor cells comprising administering a compound according to claim 1 to a mammal in need thereof for a time and under conditions effective to antagonize the $\alpha_v\beta_3$ integrin.

In addition, if it is known in the art that antagonists of $\alpha_v\beta_3$ integrin are effective to inhibit smooth muscle cell migration, the following claim may be enabled as well:

102. A method of inhibiting migration of smooth muscle cells comprising administering a

compound according to claim 1 to a mammal in need thereof for a time and under conditions effective to antagonize the $\alpha_v\beta_3$ integrin.

In addition, if it is known in the (prior) art that antagonists of $\alpha_v\beta_3$ integrin are effective to inhibit endocytosis of adenovirus by certain cell types, the following claim may be enabled as well:

103. A method of inhibiting endocytosis of adenovirus comprising the step of contacting a cell with a compound according to claim 1 for a time and under conditions effective to antagonize the $\alpha_v\beta_3$ integrin.

In addition, if it is known in the (prior) art that antagonists of $\alpha_v\beta_3$ integrin are effective to inhibit bone resorption, the following claim may be enabled as well:

104. A method of inhibiting bone resorption comprising administering a compound according to claim 1 to a mammal in need thereof for a time and under conditions effective to antagonize the $\alpha_v\beta_3$ integrin.

Notwithstanding the foregoing, claim 5 is not enabled, because it recites the term "pharmaceutical". The term "pharmaceutical" implies an intent to use the composition to treat a human disease. As such, claim 5 carries with it the implied assertion that the compounds are useful to treat human diseases.

It is stated (page 74, line 6+) that some of the claimed compounds exhibit an IC_{50} of 0.1 nM to 100 micromolar in the "293-cell" assay. Presumably the term "293-cell" is referring

(page 78, line 29+) to 293 embryonic kidney cells. However, this does not mean that there exists a human disease which can be successfully treated using the claimed compounds.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

The specification asserts (p 6, line 16+ ; p. 20, line 10) that various diseases can be successfully treated using the claimed compounds. However, in attempting to extrapolate from in vitro results to treatment of ill patients, "unpredictable" results are obtained. Consider, for example, the following:

- Nicosia (*American Journal of Pathology* 138 (4) 829-33, 1991) discloses that the peptide GRGDS is effective to inhibit angiogenesis, but that if the aspartic acid side chain is extended by just one methylene group, loss of activity results. Thus, the conclusion is that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned.

- Belo (*Inflammation* 25 (2) 91-6, 2001) discloses that thalidomide inhibited angiogenesis in mice, but failed to inhibit tumor growth in the same mouse strain.

- Mundhenke, "Tissue examination to monitor antiangiogenic therapy: a phase I clinical trial with endostatin" (*Clinical Cancer Research* 7 (11) 3366-74, 2001) disclosed the results of a phase I clinical trial with endostatin, which is an angiogenesis inhibitor.

The result is that the endostatin was not particularly effective in treating cancer patients.

- Boehm-Viswanathan (*International Journal of Molecular Medicine* 4 (4) 413-7, 1999) suggests that inhibition of angiogenesis offers the potential to effectively treat patients afflicted with cancer, but that so far success in humans has proven elusive.

- Pignatelli (*Human Pathology* 23 (10) 1159-66, 1992) discloses that in breast carcinomas, expression of integrins is downregulated. This tends to suggest that if one makes "static" assumptions about the level of expression of integrins on tumor cells, an "unpredictable" outcome is likely.

Thus, the skilled artisan would have concluded from the foregoing references that when when inhibition of angiogenesis can be achieved by a given compound "Z", success in the reduction of tumor volumes by the compound "Z" in vivo is "unpredictable". The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* 15 (3) 367-73, 1996); Kemeny (*Seminars in Oncology* 21 (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* 9 (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* 127 (4) 217-25, 2001); Garattini (*European Journal of Cancer* 37 Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* 40 (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited in vitro activity leads to "unpredictable" results. Thus, while offering hope for the future, the reference (Boehm-Viswanathan) nevertheless indicates that at the time of the invention, administration of angiogenesis inhibitors to humans suffering

from cancer would have produced "unpredictable" results.

With respect to the matter of inflammatory diseases, consider the following reference:

> Theien B. E. (*Journal of Clinical Investigation* 107 (8) 995-1006, 2001) compared the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS.

Accordingly, one cannot predict success in the treatment of inflammation based on the propensity of a compound to antagonize integrins.

On the subject of restenosis, applicants have provided no evidence that the claimed compounds will be effective to treat this disorder. Nor has any evidence been provided that, at the time of the invention, it was well known in the art that antagonists of the $\alpha_v\beta_3$ integrin will be effective in this regard. Consider the following, which pertain to restenosis:

- Gibson C. M. (*Journal of the American College of Cardiology* 32 (1) 28-34, 1998) investigated the effects of tirofiban versus placebo on the incidence of adverse cardiac outcomes and coronary artery restenosis at 6 months. Gibson found a beneficial effect at a period seven days post- angioplasty, but after 6 months, the benefit ceased to be statistically significant.

- Huckle W. R. (*Circulation* 103 (14) 1899-905, 2001) studied the effects of the

endothelin antagonist L-749,329 in an animal model of angioplasty. Huckle discloses that after 28 days of administration, mean neointimal thickness in the L-749,329-treated group was reduced by 9.0% compared with vehicle-treated controls, but that this effect was not statistically significant (P=0.13).

- Veinot J P (*Canadian Journal of Cardiology* 12 (1) 65-70, 1996) undertook a study on the efficacy of the HMGCoA reductase inhibitor lovastatin as a therapeutic agent for coronary arterial restenosis post-balloon angioplasty. The amounts of arterial injury and neointimal thickening were quantitated. A series of linear regression models was used to control for the degree of injury. It was found that the reduction of neointimal thickness for the lovastatin group compared with the control animals was 0.08 mm, a statistically significant result ($P < 0.05$). At the same time, however, the authors concluded that although lovastatin produced a statistically significant decrease in neointimal thickness post-balloon angioplasty, when extrapolated to angiographical end-points, the differences would not be clinically significant. These data suggest that lovastatin may be of marginal use in humans for limiting restenosis .

Thus, in view of the foregoing (Gibson, Huckle, Veinot), the physiological changes following an attempted therapy of restenosis may appear on the surface to be "beneficial", but on closer inspection may actually be of no significance statistically; or perhaps the physiological changes will be statistically significant at one point in time, only to become statistically insignificant at a later time; or the observed physiological changes may be statistically significant, but not "predictive" of therapeutic efficacy.

In accordance with the foregoing, “undue experimentation” would be required to use the claimed compounds to treat human disease. It is suggested that the term “pharmaceutical” be deleted from claim 5.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. §102(b) as being anticipated by Ruminski (WO 97/08145).

Ruminski discloses a genus of compounds which overlaps that which is claimed. Specific examples of compounds that fall within the scope of the instant claims can be found on each of pages 209, 621, 624, 631, 658, and 864. The fourth compound listed on page 88 (claim 4) can be found on page 621 of the reference.

Thus, the claims are anticipated.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.